## REMARKS

Claims 8-19 are pending and under examination in the above-referenced application. By this Amendment, applicant has amended claims 8 and 14 to more clearly define applicant's claimed invention. No issue of new matter is raised by these amendments. Accordingly, applicant respectfully request that the Examiner enter and consider these amendments.

**Rejection under 35 USC 103 (a)**

The Examiner rejected claims 8-19 under 35 U.S.C. 103(a) as unpatentable over Kamiya et al., in view of Bisset et al., as evidenced by Horrobin et al.

In response, the Examiner respectfully traverses the Examiner's ground of rejection. Applicant would like to point the Examiner's attention several important differences between the present invention and the disclosures of the cited prior art alone and in combination.

In the Office Action, the Examiner indicated that the composition used by Kamiya et al. may comprise phytic acid as a component as shown in paragraph 0081. However, applicant respectfully points the Examiner's attention to paragraph 0040 of Kamiya et al. which states the following:

> "The therapeutic or preventing agent for diseases caused by a decrease in the expression level of Klotho protein in animals or humans of the present invention comprises ornithine or a salt thereof, and if necessary, may comprise one or more pharmaceutically acceptable carriers, and further, an additional active ingredient for another therapeutic purpose." (Emphasis added)

and to paragraph 0053 of Kamiya et al. which states the following:

> "The feed or food and drink for the treatment or prevention of diseases caused by a decrease in the expression level of Klotho protein in animals or humans which comprises ornithine or a salt thereof as an active ingredient included feeds or foods and drinks originally containing ornithine or a salt thereof, as well as those produced by adding ornithine or a salt thereof to feeds or foods and drinks which do not contain ornithine or a

salt thereof in an ordinary process for the production of feeds or foods and drinks." (Emphasis added)

Applicant maintains that from these two paragraphs, one skilled in the art would infer that ornithine or a salt thereof is the active ingredient used in Kamiya's invention for treating or preventing a disease caused by a decrease in the expression level of Klotho protein. The remaining components are pharmaceutically acceptable carriers or additional active ingredients for another therapeutic purpose (see para. 40). Therefore, it cannot be stated that phytic acid is an active ingredient used for treating or preventing a disease caused by a decrease in the expression level of Klotho protein (e.g. ectopic calcification) since the active ingredient for treating such calcification is ornithine or a salt thereof. In order to clearly distinguish the present invention from Kamiya's disclosure, the term "as an active ingredient" has been added to claims 8 and 14 showing that the present compositions use myo-inositol hexaphosphate as an active ingredient for the claimed purpose.

Additionally, the alleged common component with the present invention "phytic acid" is indicated in its acid form when listing the possible compounds containing phosphorus used for the Kamiya's composition (see para. 0081). There is no mention about the ionic form (phytate) which is the molecular form used in the present invention. This is especially important because high-charged molecules are not easily absorbed by the skin and the present invention presents this particular advantage over the prior art.

The Examiner also stated that Kamiya et al. teach methods of treating a disease caused by a decrease in the expression level of Klotho protein (e.g. ectopic calcification) comprising administering a composition containing phytic acid by non-oral routes, citing as preferable intravenous, intraperitoneal or subcutaneous administration. Despite the general term "non-oral routes", it is not obvious to one skilled in the art at all that topical administration can be used for the compositions disclosed by Kamiya et al. since compounds with a high charge are not easily absorbed by skin as discussed above.

Accordingly, applicant maintains that topical administration is not obvious at all by making reference to the following documents where it is shown the difficulty for drugs to be delivered

transdermally. Applicant submits these documents as Exhibits to this Amendment for the Examiner's convenience.

**Kanikkannan et al.:**

Applicant points the Examiner's attention to the Abstract of Kanikkannan et al. on page 593 which reads as follows emphasizing relevant part:

*Transdermal drug delivery (TDD) is the administration of therapeutic agents through intact skin for systemic effect. TDD offers several advantages over the conventional dosage forms such as tablets, capsules and injections. Currently there are about eight drugs marketed as transdermal patches. Examples of such products include nitroglycerin (angina pectoris), clonidine (hypertension), scopolamine (motion sickness), nicotine (smoking cessation), fentanil (pain) and estradiol (estrogen deficiency).* ***Since skin is an excellent barrier for drug transport, only potent drugs with appropriate physicochemical properties (low molecular weight, adequate solubility in aqueous and non-aqueous solvents, etc) are suitable candidates for transdermal delivery****. Penetration enhancement technology is a challenging development that would increase significantly the number of drugs available for transdermal administration. The permeation of drugs through skin can be enhanced by physical methods such as iontophoresis (application of low level electric current) and phonophoresis (use of ultra sound energy) and by chemical penetration enhancers (CPE). In this review, we have discussed about the CPE which have been investigated for TDD. CPE are compounds that enhance the permeation of drugs across the skin. The CPE increase skin permeability by reversibly altering the physicochemical nature of the stratum corneum, the outer most layer of skin, to reduce its diffusional resistance. These compounds increase skin permeability also by increasing the partition coefficient of the drug into the skin and by increasing the thermodynamic activity of the drug in the vehicle. This review compiles the various CPE used for the enhancement of TDD, the mechanism of action of different chemical enhancers and the structure-activity relationship of selected and extensively studied enhancers such as fatty acids, fatty alcohols and terpenes. Based on the chemical structure of penetration enhancers (such as chain length, polarity, level of unsaturation and presence of some special groups such as ketones), the interaction between the stratum corneum and penetration enhancers may vary which will result in significant differences in penetration*

*enhancement. Our review also discusses the various factors to be considered in the selection of an appropriate penetration enhancer for the development of transdermal delivery systems.*

In addition, Kanikkannan et al. disclose at page 594, first column:

*"However, only* ***a small percentage of the drugs can be delivered transdermally due to three limitations: a). difficulty of permeation through human skin, b).skin irritation and c). clinical need.*** *The outer most layer of the skin, the stratum corneum, is an excellent barrier to almost all chemicals including drugs."* (Emphasis added)

Finally, Table 1 of Kanikkannan et al. shows a list of drugs for transdermal patches which are all non-charged or low-charged.

**Tanner and Marks:** (

Applicant points the Examiner's attention to page 250, second column, of Tanner and Marks which reads as follows emphasizing relevant part:

*"To persuade a drug to penetrate the skin and reach the systemic circulation in sufficient quantities and in the right time frame to exert a desired pharmaco therapeutic effect is no small task.* ***All substances that contact the skin penetrate to the systemic circulation to a greater or lesser extent but for the most part the great majority of xenobiotics penetrate extremely slowly – certainly insufficiently rapid to be useful from a therapeutic stand point****. The barrier to penetration is the stratum corneum (SC) and removal of this rate limiting membranous structure either by adhesive tape or by a cyanoacrylate adhesive in the skin surface biopsy technique (3) allows substances to penetrate the skin much more rapidly (4). It is worthwhile bearing in mind that the SC performs its barrier functions while in a constant state of desquamation and renewal. It is astonishing to think that this approximately 30-micron-thick structure that is continually being shed and at the same time being replenished from the epidermis on which it rests is the major protectant against environmental toxins."*

In addition, Tanner and Marks state on page 252:

*"Only a small number of drugs are actually designed for transdermal delivery. **In many cases a drug's properties, including molecular size and polarity have limited its capacity to be delivered transdermally**. Physical and chemical means of assisting transdermal delivery have been explored and some of these are discussed below."*

**Brown:**

Applicant points the Examiner's attention to the Abstracvt of Brown which reads as follows emphasizing relevant part:

*"**The protective function of human skin imposes physicochemical limitations to the type of permeant that can traverse the barrier. For a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight <500 Da. These requirements have limited the number of commercially available products based on transdermal or dermal delivery. Various strategies have emerged over recent years to optimize delivery and these can be categorized into passive and active methods**. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability. Passive methods, however do not greatly improve the permeation of drugs with molecular weights >500 Da. In contrast active methods that normally involve physical or mechanical methods of enhancing delivery have been shown to be generally superior. Improved delivery has been shown for drugs of differing lipophilicity and molecular weight including proteins, peptides, and oligonucletides using electrical methods (iontophoresis, electroporation), mechanical (abrasion, ablation, perforation), and other energy-related techniques such as ultrasound and needless injection. However, for these novel delivery methods to succeed and compete with those already on the market, the prime issues that require consideration include device design and safety, efficacy, ease of handling, and cost-effectiveness. This article provides a detailed review of the next generation of active delivery technologies."*

In addition, page 175 of Brown states: *" **Transdermal delivery is a term that should be restricted to the situation in which a solute diffuses through the various layers of the skin and into the systemic circulation for a therapeutic effect to be exerted**, e.g., treatment of withdrawal symptoms using nicotine. Dermal (topical) delivery should only be used to define a targeting to*

*the pathological sites within the skin, which involves ensuring minimal systemic absorption. Drug localization of this type is important in the treatment of dermatological conditions such as skin cancer, psoriasis, eczema, and microbial infections, where the seat of the disease is located in the skin."* (Emphasis added), and Table 1 of Brown states: "***A molecular weight less than 500 Da is essential*** *to ensure ease of diffusion across the SC (Bos and Meinardi 2000), since solute diffusivity is inversely related to its size."* (Emphasis added) Applicant notes that phytate has a molecular weight of 660 and consequently it is clear considering this document that it is not obvious at all that phytate can be absorbed by skin

Finally, Table 2 of Brown lists drugs which are compounds for passive transdermal use without charge or low charge.

**Prausnitz et al.:**

Applicant further points the Examiner's attention to Prausnitz et al. which discusses problems for administering drugs through skin and the possible solutions with penetration enhancers or other techniques. See Abstract, page 10504, first column and page 10508, second paragraph.

In view of the evidence presented above, applicant maintains that one skilled in the art would not have found that topical administration would be preferable and certainly not obvious in light of the teachings of Kamiya et al. alone or in combination with Bissett et al.

In addition, the Examiner argues that Bisset et al. teach methods of treatment for improving the visual appearance of skin comprising administering topical compositions comprising myoinositol compounds. However, applicant maintains that Bisset only discusses the cosmetic use of a composition comprising myoinositol compounds. There is no reference in the whole disclosure about a "disease" or "disorder" and the wording "cosmetically acceptable derivatives thereof" is widely used through the text (see, for example, col. 2, lines 26 and 48; col. 3, lines 11, 29 and 40; col. 9, lines 5, 6, 17, 27 and 52; col. 10, lines 29, 37, 41, 47 and 48 and also the section where the term "cosmetically acceptable carrier" is explained). Applicant points the attention of the Examiner to the definition of "cosmetic" according to the FDA U.S. Food and Drug (Federal Food, Drug and Cosmetic Act (FD&C Act), Section 201 (i) Definitions (available online:

www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChaptersIandIIShortTitleandDefinitions/ucm086297.htm)).

"Cosmetic" is defined as follows:

*"The term "cosmetic" means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap.* " (Emphasis added)

Accordingly, the use of myoinositol hexaphosphate according to Bisset et al. is a cosmetic use as can be shown by the applications mentioned in the disclosure (see col. 1 lines 10, 12-14, col. 2, lines 59-60 and list from col. 3, line 46 to col. 4, line 26) where the intended purpose is to improve the visual appearance of skin by reducing imperfections, reducing wrinkles, regulating skin smoothness, etc… .

Additionally, it should be noted that a cosmetic has a superficial effect whereas a drug for topical use has a systemic effect with all the entailed consequences in the human body. The "intended use" for a drug (present invention) and a cosmetic (Bisset et al.) is different. The intended use for a cosmetic involves a local effect, just on the surface of the skin, but it never involves a therapeutic effect as a drug does. Applicant submits herewith the following documents which also define cosmetics: Walters and Roberts, and Elsner and Maibach.

In view of the remarks above, applicant maintains that the combination of Kamiya et al and Bissett et al. does not render obvious applicant's invention because despite the teaching of the topical use of a composition with phytate of Bissett et al., this use is only cosmetic and cannot be combined with Kamiya's document since this teaches a therapeutic application.

In addition, applicant maintains that neither Bisset et al. nor Kamiya et al. disclose or suggest that phytate can be absorbed and reach the systemic circulation. On one hand, Bisset et al. is focused on a cosmetic use of phytate so that the composition used therein never reaches the systemic circulation. On the other hand, Kamiya et al. does not mention the topical administration and phytic acid is used as a carrier substance so that with Kamiya's teaching it

cannot be inferred that phytate can act as an active ingredient for treating calcifications reaching the bloodstream. Applicant submits herewith Tiwary et al. which supports the above argument. See ABstract which reads as follows emphasizing relevant part:

*"The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for* ***successfully delivering drug molecules to the systemic circulation by this route.*** *Various formulation approaches used to systemically deliver drug molecules include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Further, the adhesive mixture, physical system of the delivery system and release liner influence drug release and its permeation across the skin. In addition, great strides in designing delivery systems for maximizing percutaneous drug permeation without comprising with ease of therapy cannot be neglected in improving functionality of transdermal drug delivery systems. This article deals with the innovations pertaining to formulation and techniques as described in recent patents.*

In view of the remarks above, applicants maintain that the combination of cited references does not disclose applicants invention and would not lead on skilled in the art to use applicants invention by combining the teaching of these cited references. Accordingly, applicants maintain that claim 8-19 are not rendered obvious by the combined disclosures of Kamiya et al. and Bisset et al. and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Reconsideration and allowance of all the claims herein are respectfully requested.

Respectfully submitted,

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Aude Gerspacher
Registration No. 57,919

Cozen O'Connor
250 Park Avenue
New York, New York 10177-0030
Telephone: 212.986.1116